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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,683	03/10/2004	Charles W. Spangler	A-72170-1	8543

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DORSEY & WHITNEY LLP  
INTELLECTUAL PROPERTY DEPARTMENT  
370 SEVENTEENTH STREET  
SUITE 4700  
DENVER, CO 80202-5647

EXAMINER
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SCHLIENTZ, LEAH H

ART UNIT	PAPER NUMBER
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1618

MAIL DATE	DELIVERY MODE
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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/805,683	<b>Applicant(s)</b> SPANGLER ET AL.	
	<b>Examiner</b> Leah Schlientz	<b>Art Unit</b> 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12 March 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 8/12/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |



## DETAILED ACTION

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a trifunctional agent comprising: a) a targeting moiety, b) a medical imaging agent; and c) a photodynamic therapy (PDT) moiety. However, the claims are devoid of any structural elements that correlate to the function which is to be achieved with the claimed composition. For example, a vast number of potential “medical imaging agents” are known in the art to be capable of medical imaging. For example, such diverse structures may include microbubbles for ultrasound imaging; gadolinium chelates or superparamagnetic iron oxide nanoparticles for MRI; barium sulfate powder for x-ray imaging; various radionuclide chelates or microspheres for PET imaging, etc. Furthermore, a very large number of “photodynamic therapy moieties” are known. Applicant has identified in the instant specification several generic types

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of imaging agents and photodynamic therapy agents. Applicant has demonstrated a limited number of examples of a trifunctional agent that demonstrate the claimed components, e.g. see Figures 4 and 5, describing specific targeting moiety, porphyrin and chromophores. Therefore, it is clear that Applicant had possession of such a specific formulation at the time of filing as identified in Figures 4 and 5, but the specification as originally filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed trifunctional agent, one would have to determine the type of targeting moiety to conjugate to which out of an almost unlimited number of potential "imaging agents" and "pdt moieties" should be combined into a single agent, and further which out of an almost unlimited number of potential functional groups or chemical reactions would be necessary to derivatize and conjugate the moieties into a single agent having the claimed functional properties. One would have to select which portions of which molecules would be suitable to be conjugated to the others and on what positions of the molecules with various substituents. Applicant's limited disclosure of a particular compound which has the claimed functional properties does not provide support that Applicant envisaged the invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an indication of what the agent does, rather than what it is. See MPEP 2163 and *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Dees *et al.* (WO 00/25665, whereby US 6,493,570 is relied upon as equivalent).

Dees discloses methods of imaging and treatment using at least one photodynamic therapy (PDT) agent (abstract). One embodiment includes the steps of administering a photo-active agent, the photoactive agent being retained in diseased tissue; and treating the tissue with light sufficient to photoactivate the photo-active agent in the diseased tissue. Preferably the photo-active agent is a halogenated xanthene such as Rose Bengal. In a further embodiment, the photoactive agent is capable of acting as a contrast agent for CAT scanning, fluorography, MRI, etc. (column 3, lines 10-53). The facility with which the halogenated xanthenes target specific tissues can be optimized with attachment

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of specific functional derivatives at positions  $R^1$  and  $R^2$ , such as DNA, RNA, amino acid, antibodies, etc. (column 5, lines 53+). The halogenated xanthenes have desirable SPE (single photon excitation) and TPE (two photon excitation) characteristics (column 6, lines 53+). The chemical structure of the halogenated xanthenes, which have high electron density due to their significant halogen content, renders them opaque to x-rays (column 8, lines 28-63). See also claim 11. Accordingly, the halogenated xanthenes having targeting moieties attached thereto meet the instant claims because the iodinated portion of the molecule acts as a "medical imaging agent" (i.e. for x-ray imaging), and the xanthene portion of the molecule acts as a "photodynamic therapy moiety," as claimed. With regard to claim 2, a "linker" would inherently be present since Dees teaches conjugation of a targeting moiety at positions  $R^1$  and  $R^2$ .

Claims 1-5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Achilefu *et al.* (US 6,217,848).

Achilefu discloses dye-peptide conjugates useful for diagnostic imaging and therapy. The molecules are useful for endoscopic applications for the detection of tumors and other abnormalities and for localized therapy and photoacoustic tumor imaging, detection and therapy (abstract). The cyanine dye bioconjugates have the general formula as shown in Formula 1, column 2. The biomolecule,  $B_m$  may be any bioactive peptide, drug, hormone, etc. (column 2, lines 42-45). More specifically  $B_m$  is a tumor specific biomolecule or drug mimic selected from peptides or oligosaccharides containing 2-50 monomer units and

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including somatostatin, bombesin, neurotensin, etc. (column 5, lines 5-9). In a preferred embodiment, a therapeutic procedure comprises attaching a porphyrin to a bioconjugate and using it for photodynamic therapy or shining light of a specific wavelength on the dipeptide conjugate to achieve a photodynamic therapy effect (column 5, lines 55-60). Regarding claim 2, the biomolecule is linked to the dye. Regarding claim 5, any porphyrin has at least some "substitution" (e.g. at least hydrogen, etc.).

Claims 1-5 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Achilefu *et al.* (US 6,761,878).

Achilefu discloses novel tumor specific phototherapeutic and photodiagnostic agents. The compounds consist of a carbocyanine dye for visualization, photosensitizer for photodynamic treatment, and tumor receptor-avid peptide for site-specific delivery of the probe and phototoxic agent to diseased tissues. A combination of these elements takes full advantage of the unique and efficient properties of each component for an effective patient care management (abstract). Exemplary compounds include peptide-dye-phototherapy conjugates shown in Examples 6-8. The targeting peptide is octeotide, the dye is a carbocyanine dye (chromophore) and the photosensitizer is HPPH. See also Fig. 1B-D. In one embodiment, a porphyrin or photodynamic therapy agent may be attached to a bioconjugate and then light is administered of an appropriate wavelength for detecting and treating an abnormality (column 7, line 66-column 7, line 2). Regarding claim 2, the biomolecule and/or

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phototherapeutic agents are linked to the dye. Regarding claim 5, any porphyrin has at least some "substitution" (e.g. at least hydrogen, etc.).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Achilefu *et al.* (US 6,761,878), in view of Karotki (*IEEE J. Selected Topics in Quant. Electronics.*, 2001, 7(6), p. 971-975).

Achilefu discloses novel tumor specific phototherapeutic and photodiagnostic agents. The compounds consist of a carbocyanine dye for visualization, photosensitizer for photodynamic treatment, and tumor receptor-

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avid peptide for site-specific delivery of the probe and phototoxic agent to diseased tissues, as set forth above. A porphyrin may be used as a PDT agent.

Achilefu does not specifically teach that the porphyrin is a two photon absorption PDT agent.

Karotki teaches a new porphyrin photosensitizer whose two-photon absorption cross section has been considerably enhanced by chemical design (abstract). See Figure 2(a). Karotki teaches to make pDT more generally applicable, it is crucial to delivery light deeper into tissue. This may be achieved by utilizing the nonlinear optical effect oof tow-photon abosprtion in which case the illumination is carried out at near-infrared (IR) wavelengths where the tissue is significantly more transparent than in the visible. However, so far TPA of tumor-specific porphryins have been notoriously inefficient. The new porphyrin photosensitizer with an enhanced TPA cross section has the ability to generate singlet oxygen upon illumination with near-IR light (page 971). The novel porphyrin may be employed in new tumor-specific drugs with a large TPA cross-section which may eventually lead to PDT-based treatment of deep tumors (page 974).

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ the porphyrin disclosed in Figure 2(a) of Karotki as the photosensitizer in the conjugates of Achilefu. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Achilefu teaches that his conjugates are useful for diagnosis and photodynamic therapy of tumor, and teaches porphyrin as the photodynamic

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therapy agent, and because Karotki teaches that his novel porphyrin has an enhanced TPA cross-section which is superior to previous porphyrin photosensitizers. One would have had a reasonable expectation of success in doing so because Karotki teaches that to make PDT more generally applicable, it is critical to deliver light deeper into tissue which may be achieved by TPA, and because the novel porphyrin may be employed in new tumor-specific drugs with a large TPA cross-section which may eventually lead to PDT-based treatment of deep tumors.

### ***Conclusion***

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/  
Supervisory Patent Examiner, Art Unit 1618

LHS